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No. 06-1249

IN THE
Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI TO THE
SUPREME COURT OF VERMONT

BRIEF OF *AMICI CURIAE* ANJU BUDHWANI, M.D.; CURT D. FURBERG, M.D., PH.D.; ARTHUR AARON LEVIN, M.P.H.; RAHUL SHARMA, M.D., M.B.A.; CANTON ELECTRICAL WELFARE FUND OF THE IBEW, LOCAL 540; HEALTH & WELFARE FUND OF THE DEA, NYPD; RETIREE HEALTH & WELFARE FUND OF THE DEA, NYPD; AND OHIO CARPENTERS HEALTH FUND IN SUPPORT OF RESPONDENT

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CASES

44 Liquormart v. R.I., 517 U.S. 484 (1996) 27

Geier v. American Honda Motor Co., 529 U.S. 861 (2000) 25

McEwan v. Ortho Pharmaceutical Corp., 528 P.2d 522 (Or. 1974) 29

Riegel v. Medtronic, Inc., 128 S. Ct. 999 (2008) 35

Thompson v. W. States Med. Ctr., 535 U.S. 357 (2002) 27

STATUTES AND REGULATIONS

Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) 8

Food and Drug Administration Amendments Act of 2007, Pub. L. 110-85, 121 Stat. 823 (2007) ... 31

Food, Drug, & Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938) 6

21 C.F.R. §314.80 ..... 18, 23, 25

21 C.F.R. §201.57 ..... 23, 25, 27

Cited Authorities

Page

Conn. Agencies Regs. §19-13-D72 12

Md. Regs. Code tit. 10, §.27.20.06 11

LEGISLATIVE MATERIALS

FDA, Merck and Vioxx: Putting Patient Safety First? Hearing Before the S. Comm. on Finance, 108th Cong. 14 (2004) 34

S. Rep. No. 87-1744 (1962) 7

ADMINISTRATIVE MATERIALS

31 Fed. Reg. 9426 (1966) 8

35 Fed. Reg. 11,273 (1970) 8

44 Fed. Reg. 37,434 (1979) 28, 29

45 Fed. Reg. 32,550 (1980) 9

71 Fed. Reg. 3922 (2006) 26, 28

73 Fed. Reg. 2848 (2008) 23, 24, 28

Center for Drug Evaluation and Research, *Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (March 2005) 18, 19, 23

Cited Authorities

Page

Center for Drug Evaluation and Research, *Manual of Policies and Procedures* (July 2, 2003) 29

Food and Drug Administration, *Early Communication About an Ongoing Safety Review* (Nov. 14, 2007) 30

Food and Drug Administration, *Early Communication About an Ongoing Safety Review* (Feb. 2008) 30

Food and Drug Administration, *FDA Studying Potential Safety Issues with Several Drugs* (June 2008) 30

Food and Drug Administration, *Preventing Medical Errors: Severe Tissue Injury with IV Promethazine* (Dec. 2006) 17

Food and Drug Administration, *Severe Tissue Injury with IV Promethazine (December 2006)* (Feb. 2008) 17

Institute of Medicine of the National Academies, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (2007) .. 25, 36

Letter from Hon. Henry Waxman et al., to Hon. Andrew C. von Eschenbach, M.D. (Jan. 23, 2008) (FDA Docket No. 2008N-0032-0022) ... 28

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Letter from Stephen Mason, FDA, to Hon. Henry Waxman (Mar. 7, 2008) (FDA Docket No. 2008N-0021) 28

BOOKS AND PERIODICALS

R.W. Baxter, et al., *Three Phenothiazine Derivatives in Anesthesia*, 9 Anaesthesia 79 (1954) 7

David Brown, *Maker of Vioxx is Accused of Deception*, Wash. Post, Apr. 16, 2008, at A1 ... 34

Troy E. Brown & Dwain L. Eckberg, *Promethazine Affects Autonomic Cardiovascular Mechanisms Minimally*, 282 J. Pharmacology & Experimental Therapeutics 839 (1997) 5

Julie M. Donahue, *A Decade of Direct-to-Consumer Advertising of Prescription Drugs*, 357 New Eng. J. Med. 673 (2007) 35, 36

F.R. Ernst & A.J. Grizzle, *Drug-Related Morbidity and Mortality: Updating the Cost-of-Illness Model*, 41 J. Am. Pharmaceutical Ass'n 192 (2001) 32

Phil B. Fontanarosa et al., *Postmarketing Surveillance - Lack of Vigilance, Lack of Trust*, 292 JAMA 2647 (2004) 21

Cited Authorities

Page

B.N. Halpern & R. Ducrot, *Experimental Research on a New Series of Chemical Substitutes with Powerful Antihistaminic Activities: The Phenothiazine Derivatives*, 140 Comp. Rend. Soc. Biol. 361 (1946) 4

Katherine A. Helm, *Protecting Public Health From Outside the Physician's Office*, 18 Fordham Intell. Prop. Media & Ent. L.J. 117 (2007) 6-7

Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, 60 Admin. L. Rev. 431 (2008) 9

Teresa Finlay, *Intravenous Therapy* (2004) ... 11, 13

Stanton A. Glantz, *Primer of Biostatistics* (5th ed. 2002) 20

Julie Golembiewski & Sheri Tokumaru, *Pharmacological Prophylaxis and Management of Adult Postoperative/Postdischarge Nausea and Vomiting*, 21 J. PeriAnesthesia Nursing 385 (2006) 5

Susan Hohenhaus, *An Informal Discussion of Emergency Nurses' Current Clinical Practice*, 31 J. Emergency Nursing 465 (2005) 16

Cited Authorities

Page

Kris Hundley, *Drug Warnings Fall Flat*, St. Petersburg Times, Aug. 5, 2007, at 1A ... 34

Institute for Safe Medication Practices, *Action Needed to Prevent Serious Tissue Injury with IV Promethazine* (Aug. 10, 2006) 15, 16, 17, 22

Institute for Safe Medication Practices, *Promethazine Conundrum: IV Can Hurt More than IM Injection!* (Nov. 2, 2006) . 15, 16, 17

Amalia M. Issa, et al., *Drug Withdrawals in the United States: A Systematic Review of the Evidence and Analysis of Trends*, 2 Current Drug Safety 177 (2007) 21, 33

Chiaki Kamei & Kenji Tasaka, *Participation of Histamine in the Step-Through Active Avoidance Response and its Inhibition by H1-Blockers*, 57 Japanese J. Pharmacology 473 (1991) 4-5

Sandra Kane-Gill et al., *Adverse-Drug-Event Rates for High-Cost and High-Use Drugs in the Intensive Care Unit*, 63 Am. J. Health-Sys. Pharmacy 1876 (2006) 31

Elizabeth Kassner, *Evaluation and Treatment of Chemotherapy Extravasation Injuries*, 17 J. Pediatric Oncology Nursing 135 (2000) .. 13

Cited Authorities

Page

John R. Keene, et al, *Accidental Intra-arterial Injection: A Case Report, New Treatment Modalities, and a Review of the Literature*, 64 J. Oral and Maxiollofacial Surgery 965 (2006) 12, 15

R.L. Kravitz & R.A. Bell, *Direct-to-Consumer Advertising of Prescription Drugs: Balancing Benefits and Risks, and a Way Forward*, 82 Clinical Pharmacology & Therapeutics 360 (2007) 35-36

Erika Lietzan, *Advisory Committees at FDA*, 39 J. Health L. 415 (2006) 8

Geraldine Light, et al, *Promethazine (Phenergan) as an Adjunct to Anesthesia*, 164 JAMA 1648 (1957) 7

Mark A. Malesker et al., *Extravasation of I.V. Promethazine*, 56 Am. J. Health-Sys. Pharmacy 1742 (1999) 15

Dennis Mangano et al., *The Risk of Aprotinin in Cardiac Surgery*, 354 New Eng. J. Med. 353 (2006) 33

Thomas J. Moore et al., *Serious Adverse Drug Events Reported to the Food and Drug Administration, 1998-2005*, 167 Archives Internal Med. 1752 (2007) 32

Page

Susan Paparella, *The Dangers of Intravenous Promethazine Administration*, 33 J. Emergency Nursing 53 (2007) 5, 15, 16

Physicians' Desk Reference (35th ed. 1981) ... 9

Random House Webster's Unabridged Dictionary (2d ed. 2001) 20

Max Sadove, *Promethazine in Surgery*, 162 JAMA 712 (1956) 7

Carmel Sauerland et al., *Vesicant Extravasation Part I*, 33 Oncology Nursing F. 1134 (2006) 12, 13, 14

Bonnie L. Senst et al., *A Practical Approach to Determining Costs and Frequency of Adverse Drug Events in a Health Care Network*, 58 Am. J. Health-Sys. Pharmacy 1126 (2001) 31, 32

Mike Stobbe, *2 More Studies Link Drug to Deaths*, Deseret Morning News, Feb. 21, 2008, at A6 34

Brian Strom, *Pharmacoepidemiology* (3d ed. 2000) 19, 20

Page

Eric J. Topol, *Failing the Public Health — Rofecoxib, Merck, and the FDA*, 351 New Eng. J. Med. 1707 (2004) 34

Sharon M. Weinstein, *Plumer's Principles & Practice of Intravenous Therapy* (8th ed. 2007) 5, 11, 12, 13

OTHER MATERIALS

Baxter Pharm., *Phenergan Injection* (2005) ... 6

Cincinnati Children's Hospital Medical Center, *Vesicant Chemotherapy Extravasation* (June 2003) 14

Carmen DeNavas-Walt, et al., U.S. Census Bureau, *Income, Poverty, and Health Insurance Coverage in the United States: 2006* (Aug. 2007) 33

A. Elixhauser and P. Owens, *Adverse Drug Events in U.S. Hospitals*, HCUP Statistical Brief #29 (Apr. 2007) 31

Int'l. Fed'n. of Pharm. Mfrs. and Ass'ns., *Medical Dictionary for Regulatory Activities Introductory Guide Version 11.0* (2008) 22

Page

Kaiser Family Foundation, *National Health Expenditures Per Capita*, 1995-2006 (May 2008) 33, 35

Kaiser Family Foundation, *Profitability of Pharmaceutical Manufacturers Compared to Other Industries, 1995-2006* (Jan. 2008) 35

Oregon State Board of Nursing, *Advisory Guidelines for Infusion Therapy* (Sept. 20, 2001) 14

Aimee S. Payne et al., *Chemotherapy Extravasation Injury,* UpToDate (Sept. 2007) 12-13

U.S. Dep't of Veterans Affairs, VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel, *National PBM Drug Guidance: Promethazine HCL Injection* (Feb. 2007) 17

University of New Mexico Hospitals, *Chemotherapy* (July 2000) 14

Utah University Health Care, *Promethazine (Phenergan) Injection Classified as Vesicant* (Apr. 2005) 17

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INTEREST OF AMICI CURIAE [1]

Healthcare Amici are health care providers, educators, and public health advocates. Their professional responsibilities require that they balance the risks of various pharmaceuticals against their therapeutic benefit, and that they assess the impact of the conduct of the pharmaceutical industry on public health. Amici have a professional interest in ensuring that the public health is protected through laws and public policies.

Third-Party Payor Amici are self-insured union health plan funds, each of which is administered by trustees. The trustees collectively manage an aggregate $61 million in plan assets that are used to provide health insurance and pharmaceutical benefits for over 62,000 current and former union members and their beneficiaries. As health insurers, amici ultimately provide coverage when plan participants experience adverse reactions to their medication. If these reactions can be shown to have been caused by a manufacturer's failure to warn of foreseeable risks, amici have the right to recoup their costs by exercising subrogation and reimbursement rights. These provisions are critical cost-saving measures in the face of rapidly increasing healthcare prices, and help self-insured plans keep down

[1] No counsel for a party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than the *amici curiae*, or their counsel, made a monetary contribution to its preparation or submission. The parties have filed waivers consenting to the filing of all *amicus* briefs.

health insurance costs. The matters under review by this Court directly affect amici's ability to recoup expenses associated with unreasonably unsafe medication.

SUMMARY OF ARGUMENT

Phenergan, the brand name for the generic compound promethazine hydrochloride, was approved for sale in 1955. Phenergan has a low "pH," meaning that it is acidic and highly damaging to human tissue. At the time the Food and Drug Administration ("FDA") approved Wyeth's new drug application, safety reviews were far more cursory than they are today, and they did not involve "balancing" a drug's risks against its expected benefits. In the years following Phenergan's approval, FDA reviews of the drug were of limited scope, and there is no evidence that Wyeth ever submitted, or that FDA considered, comprehensive analyses of the frequency and severity of injuries associated with Phenergan.

Intravenous medications like promethazine may be administered by IV push or IV drip. IV push administration is more likely to result in "extravasation," the inadvertent administration of medication outside the vein and into surrounding tissues. Because extravasation is not rare, the medical profession classifies drugs by their potential to cause injury if they extravasate. Most drugs are relatively safe, and extravasation is not serious. Some drugs, like promethazine, are classified as "irritants." Irritants cause pain and swelling when they extravasate, but do not usually cause permanent damage. The most dangerous drugs, classified as "vesicants," can cause tissue necrosis and gangrene, among other serious injuries. Hospitals create special policies for the administration of

vesicants, including, in some instances, limitations on IV push administration. As an irritant, however, promethazine has not been subject to these policies; promethazine has usually been administered by nurses via IV push, with none of the precautions associated with vesicants. Only recently have the dangers of promethazine been publicized, and FDA has now twice posted warnings about IV administration of promethazine on its website, identifying it as a "known vesicant" despite its labeling.

Although there are few published reports of injuries caused by promethazine, it is possible to analyze individual reports of injuries in the FDA's database. This analysis demonstrates that between November 1997 and December 2006, reported injuries associated with promethazine were thirty times more likely to involve gangrene or amputation than injuries associated with other intravenous drugs. Yet there is no evidence that Wyeth ever conducted an analysis of the frequency of these injuries, or submitted an analysis to FDA.

The story of Phenergan thus serves as a cautionary tale of how insufficient manufacturer vigilance, coupled with lax regulatory oversight, can cause serious injuries to patients. Nor is Phenergan an isolated example. On average, 1.5 drugs per year were withdrawn over safety concerns between 1993 and 2006. Anecdotal reports of particular drugs withdrawn from the market – for safety problems foreseeable years earlier – suggest that unreasonably unsafe medication causes large numbers of fatalities, and that associated costs can run into billions of dollars. As many as 30% of hospitalized patients may experience an adverse drug event, and such patients are likely to see costs increase by $1,900 to $7,000.

These costs are ordinarily borne by patients and their insurers. However, when an adverse drug reaction is caused by the manufacturer's failure to warn of foreseeable risks, third party payors' reimbursement and subrogation rights can serve as a powerful cost-containment mechanism that helps keep down health insurance costs. If this Court holds that state tort claims are preempted by FDA regulations, neither patients nor insurers will be able to shift the costs of injuries to the drug manufacturers who, with their superior information about, and control over, their products, are in the best position to avoid them. Ultimately, all consumers will pay the price in higher costs for basic healthcare.

ARGUMENT

I. PHENERGAN AND INTRAVENOUS ADMINISTRATION

A. Phenergan and its History with FDA

Phenergan is the brand name for promethazine hydrochloride, a compound first synthesized in 1946. *See* B.N. Halpern & R. Ducrot, *Experimental Research on a New Series of Chemical Substitutes with Powerful Antihistaminic Activities: The Phenothiazine Derivatives*, 140 Comp. Rend. Soc. Biol. 361 (1946) *(Fr.)*. Promethazine belongs to a class of drugs known as "H1 blockers," which means that it is an antihistamine that operates by blocking the ability of the body's neurons to respond to the presence of the neurotransmitter histamine. *See* Chiaki Kamei & Kenji Tasaka, *Participation of Histamine in the Step-Through Active Avoidance Response and its Inhibition by*

H1-Blockers, 57 Japanese J. Pharmacology 473 (1991); Troy E. Brown & Dwain L. Eckberg, *Promethazine Affects Autonomic Cardiovascular Mechanisms Minimally*, 282 J. Pharmacology & Experimental Therapeutics 839 (1997). Promethazine also acts as a D2 and M1 blocker, meaning that it blocks neurons from responding to the neurotransmitters dopamine and acetylcholine. By blocking histamine, dopamine, and acetylcholine, promethazine can prevent these neurotransmitters from exerting various effects, such as activating the brain areas that control vomiting and nausea. *See* Julie Golembiewski & Sheri Tokumaru, *Pharmacological Prophylaxis and Management of Adult Postoperative/Postdischarge Nausea and Vomiting*, 21 J. PeriAnesthesia Nursing 385 (2006). Promethazine is thus used to treat, among other things, allergic reactions, nausea, and motion-sickness. *See* JA390.

Promethazine is available in tablets, suppositories, and cough syrup, in addition to the injectable form at issue here. In its injectable form, promethazine has a pH of 4 to 5.5. JA390. pH, or "potential of hydrogen," is a 0 to 14 scale that measures the acidity or alkalinity of a solution. Water, a neutral solution, has a pH of 7. Human body fluids typically have a pH of around 7.4. *See* Sharon M. Weinstein, *Plumer's Principles & Practice of Intravenous Therapy* 99-100 (8th ed. 2007). Promethazine, with its low pH, is, essentially, an acid, and also contains an additional irritating substance, which is why it can cause such damage. *See* JA94; Susan Paparella, *The Dangers of Intravenous Promethazine Administration*, 33 J. Emergency Nursing 53, 54 (2007). In worst case scenarios, Phenergan damages an

artery, cutting off blood flow to the surrounding areas, with resulting tissue necrosis, gangrene, and, ultimately, amputation. JA72. In other cases, Phenergan may not reach an artery, but may still cause very serious injuries, such as nerve damage, phlebitis and thrombophlebitis (vein inflammation and inflammation with clotting), abscesses, and tissue necrosis, requiring skin grafts and fasciotomy (cutting of connective tissue). *See* Baxter Pharm., *Phenergan Injection* ("Baxter Label") (2005), http://www.baxter.com/products/anesthesia/anesthetic_pharmaceuticals/downloads/ phenergan.pdf (listing injuries that can occur "regardless of the route of administration").[2]

Phenergan was first approved for sale in its injectable form in 1955. JA266-67. At that time, prior to the 1962 Kefauver-Harris Amendments to the Food, Drug, & Cosmetic Act ("FDCA"), FDA was empowered to review drugs for safety but not efficacy. *See* FDCA, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1052 (1938). If FDA took no action within 180 days of a new drug application, the application would automatically become effective. *Id*. There was no review to determine whether the drug was efficacious for its intended uses, and thus, necessarily, there was no balancing of risks relative to benefits. The safety reviews of that time were far more cursory than those conducted today; only after the 1962 amendments were more stringent requirements enacted, such as the requirement that manufacturers conduct well-controlled trials in three phases. *See* Katherine A. Helm, *Protecting Public Health From*

[2] In 2002, Baxter Healthcare Corporation acquired the division of Wyeth that manufactured the injectable form of Phenergan; the labeling was subsequently revised.

Outside the Physician's Office, 18 Fordham Intell. Prop. Media & Ent. L.J. 117, 129 (2007). Though the 1962 amendments still allowed for automatic approval if FDA took no action, in practice, after 1962, FDA routinely requested additional information within the prescribed period, thus delaying approval substantially. *Id.* at 130 n.40.

As a result of the pre-1962 system, not only did Phenergan receive a less stringent safety review than would have occurred today, but there is no evidence that FDA considered the risks of intravenous relative to intramuscular administration, let alone the distinction between IV drip and IV push. At around the time of FDA's approval, published studies of Phenergan typically did not compare the safety of different forms of administration (oral, intramuscular, intravenous), nor did they distinguish between IV push and IV drip. *E.g.*, Geraldine Light, et al, *Promethazine (Phenergan) as an Adjunct to Anesthesia*, 164 JAMA 1648 (1957); Max Sadove, *Promethazine in Surgery*, 162 JAMA 712 (1956); R.W. Baxter, et al., *Three Phenothiazine Derivatives in Anesthesia*, 9 Anaesthesia 79 (1954). Wyeth did not introduce any evidence at trial suggesting that it supplied FDA with comparisons of the safety of various modes of administration. Thus, there is no reason to believe that any such studies were presented to FDA prior to Phenergan's approval.

There is similarly no reason to believe that Phenergan's safety was revisited by FDA after the 1962 FDCA amendments. With these amendments, Congress directed FDA to review the efficacy, as well as the safety, of new drugs. *See* S. Rep. No. 87-1744, at 9-10 (1962).

The new statutory provisions required FDA to determine whether drugs that had been approved between 1938 and 1962 – and thus had never been reviewed for efficacy – were effective for their indications. *See* Pub. L. No. 87-781, §107, 76 Stat. 780, 788-89 (1962). At the time of the Act's passage, FDA had fewer than a dozen physicians on staff and thus could not make efficacy determinations on its own; instead, it contracted with the National Academy of Sciences ("NAS") to conduct the reviews in a program that would be known as the Drug Efficacy Study Implementation ("DESI") Review. *See* Erika Lietzan, *Advisory Committees at FDA*, 39 J. Health L. 415, 420 (2006). FDA directed that all holders of new drug applications approved between 1938 and 1962 submit to the NAS various types of information, including a "[l]ist of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, package insert, or brochure," as well as unpublished articles on the same topic. 31 Fed. Reg. 9426, 9426 (1966).

To conduct the reviews, "[t]he NAS, not FDA, selected the experts who served on the [DESI] panels. Meetings were closed to the public, and indeed to FDA, and neither the date nor the location was announced in advance." Lietzan, *supra*, at 420 n.18. If the drug was evaluated as effective, the manufacturer supplied FDA with an amended label, after which time "new-drug applications which became effective on the basis of safety prior to October 10, 1962, will be approved on the basis of effectiveness as well as safety of the drug." 35 Fed. Reg. 11,273, 11,273 (1970). Thus, nothing in the DESI program — or the record in this case — suggests

that FDA had any reason to revisit Phenergan's safety as part of the post-1962 drug reevaluations.[3]

In the mid-1970s, FDA requested revisions to Phenergan's labeling, including to the warnings concerning intra-arterial injection. JA270-296. However, once again, there is no evidence that Wyeth supplied FDA with any studies or analyses concerning the frequency or severity of injuries associated with intravenous administration generally, or specifically comparing injury rates of IV push and IV drip.

In 1980, FDA initiated its Labeling Format Revision Program. *See* 45 Fed. Reg. 32,550 (1980). At that time, the Phenergan label contained almost the same language concerning intra-arterial administration that would exist on the 2000 label at the time of Respondent's injuries. *Compare* Phenergan Injection, in *Physicians' Desk Reference* 1946-48 (35th ed. 1981) *with* JA390. Wyeth submitted a supplemental application to conform its label to the new format in 1981, and over a period of 17 years, Wyeth and FDA intermittently exchanged correspondence on the subject. JA297-354. During this process, FDA requested revisions to the warnings regarding inadvertent intra-arterial administration. JA309-19. Correspondence sometimes halted for years and, on at least two occasions, FDA apparently lost track of the status of Wyeth's labeling and application. JA347; JA353 (Wyeth supplies FDA with "administrative

[3] DESI took years to complete. Approximately 20 drugs approved between 1938 and 1962 remain on the market today without a final determination of effectiveness. *See* Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, 60 Admin. L. Rev. 431, 447 (2008).

record" of Wyeth's supplemental application; Wyeth provides FDA with "narrative" comparing 1992 and 1996 labels).

Finally, in February 1997, FDA approved Wyeth's supplemental application conditioned on Wyeth further amending the draft label. JA357. Regarding inadvertent intra-arterial injection, the letter stated "Retain verbiage in current label," an apparent reference to the language on the 1996 label that had existed unchanged since at least 1980. JA359. No reference was made to earlier reviewers' requests for amendments, and no reasons were offered for FDA's reversal, although the United States now offers that FDA believed its earlier changes to be "non-substantive." U.S. Br. 25. Wyeth submitted a new label in 1998, and later that year, FDA completed its review. JA382. There is no evidence in the record suggesting that during this 17-year-process, Wyeth ever supplied FDA with any analysis or review of Phenergan's safety profile, nor is there evidence that FDA requested or reviewed such data.

Thus, given the cursory requirements of the 1938 regime, the limited scope of the DESI program, and a labeling review process that did not apparently involve any quantitative examinations of Phenergan's safety, nothing in the record suggests that Wyeth ever submitted to FDA comprehensive analyses concerning the safety of the injectable form of Phenergan – or concerning the frequency or severity of injuries associated with intravenous administration – at any time in Phenergan's 53-year history.

B. Procedures for Intravenous Administration; Classification of Phenergan as an "Irritant"

In most intravenous administrations, the clinician uses a metal needle covered by a plastic sheath, or catheter, to pierce the vein. The needle is removed, leaving the catheter partly buried within the vein. *See* Weinstein, *supra*, at 221. The infusion set, a length of flexible tubing ("line"), connects the catheter to a fluid container, such as a plastic bag or syringe. *See id.* at 224-225, 267. Medication can be administered through the infusion set via "IV drip," or can be injected into the vein via "IV push." IV push administration can be accomplished by injecting the drug into the infusion set or tubing, or into the catheter. *See* Weinstein, *supra*, at 479. For some medications, the clinician may choose to use a butterfly infusion set, where medication is delivered through tubing attached to a needle, rather than through a catheter. JA46-48.

Before needle insertion, the clinician decides whether to use a peripheral vein or a central vein. Peripheral veins are located in the extremities, and most IV medications are administered through the veins of the hands and arms. *See* Teresa Finlay, *Intravenous Therapy* 38 (2004). Central veins are located in the neck and chest cavity. *Id.* at 40-41. Peripheral vein infusion is a task performed by registered nurses. *See* Weinstein, *supra*, at 7-8. Central venous administration, by contrast, must be ordered by a physician, and under many state regulations (and/or hospital policies), nurses may not insert central lines. *Id.* at 289; *see* Md. Regs. Code tit. 10, §.27.20.06 (nurses with special training may remove, but not place, central catheters);

Conn. Agencies Regs. §19-13-D72 (nurses may only insert central catheters placed through a peripheral vein, and only with special training).

One of the risks associated with IV administration is "extravasation," or inadvertent administration of medication outside the vein and into surrounding tissues. *See* Carmel Sauerland et al., *Vesicant Extravasation Part I*, 33 Oncology Nursing F. 1134 (2006). There are many reasons a drug might extravasate, such as improper needle placement or dislodgment of the catheter or needle. *E.g.*, JA67, 70-71. Extravasation is less likely to occur during IV drip because improper catheter placement halts the flow of IV drip fluid, alerting the clinician. Additionally, the needle of the winged infusion set often used for IV push is more likely to become dislodged or damage the vein than would the soft catheter typically used in IV drip. JA67-71; *see* John R. Keene, et al, *Accidental Intra-arterial Injection: A Case Report*, *New Treatment Modalities*, *and a Review of the Literature*, 64 J. Oral and Maxiollofacial Surgery 965, 967 (2006) (recommending IV drip to avoid extravasation).

Because extravasation is not uncommon, JA73, 75-76; Weinstein, *supra*, at 154, the medical profession classifies intravenous drugs by their potential to cause injury. Most drugs are relatively harmless, and extravasation is not a serious event. *See* Weinstein, *supra*, at 154. Some drugs, classified as "irritants," may cause inflammation and pain, but do not result in tissue necrosis or long-term damage. "Vesicant" drugs, however, may cause tissue necrosis, gangrene, and severe or permanent injuries. *See* Aimee S. Payne et

al., *Chemotherapy Extravasation Injury*, UpToDate (Sept. 2007), http://www.uptodate.com/home/index.html; Sauerland, *supra*, at 1134-35.[4] Although the distinction between vesicants and irritants is not always a bright line,[5] extravasation of drugs classified as vesicants in particular is a "medical emergency." Elizabeth Kassner, *Evaluation and Treatment of Chemotherapy Extravasation Injuries*, 17 J. Pediatric Oncology Nursing 135, 139 (2000).[6]

Consequently, clinicians are instructed to take special precautions when administering drugs classified as vesicants. For example, one common recommendation is that vesicants be administered through central veins, because central veins' larger size makes extravasation less likely.[7] *See* Finlay, *supra*, at 42, 75; Sauerland, *supra*,

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[4] UpToDate is an online medical research database that is commonly used as a basic reference guide by physicians

[5] Some irritants may occasionally be associated with tissue destruction. As Payne explains, "As an example, there is one case report of tissue necrosis from an extravasation of oxaliplatin, although another series of 11 patients showed no tissue destruction. In such cases, the extent of tissue injury may be a function of the amount of drug extravasated." Payne, *supra*; *see* Sauerland, *supra*, at 1135 (reporting that the irritant Cisplatin has vesicant potential if it extravasates in large quantities).

[6] Vesicants are commonly associated with chemotherapy, and are often discussed in the oncology context, where the risks and benefits of administration may differ from other contexts.

[7] By contrast, one author recommends central venous administration for irritants only if the infusion will be "continuous," *see* Finlay, *supra*, at 75, which, in medical jargon, means a period exceeding two hours, *see* Weinstein, *supra*, at 479.

at 1139 (describing central IV as the "preferred route of administration" for vesicants). Clinicians are sometimes instructed to use plastic needles, because metal can damage veins. *See* Sauerland, *supra*, at 1136. Some hospitals limit who may administer vesicants and by what method. *See*, *e.g.*, University of New Mexico Hospitals, *Chemotherapy* (July 2000), http://hospitals.unm.edu/policies_and_procedures/ (select Pharmacy, Chemotherapy) (vesicants may only be administered by central lines; IV push of vesicants via peripheral line only permissible by an oncology-certified nurse); Cincinnati Children's Hospital Medical Center, *Vesicant Chemotherapy Extravasation* (June 2003), http://www.cincinnatichildrens.org/ed/cme/ed-services/policies.htm (special training required to administer vesicants). Clinicians are directed not to administer vesicants in the antecubital region at the bend of the elbow – the site used for Respondent's IV infusion, JA69-70 – because the needle or catheter can easily become dislodged, and because the proximity to arteries heightens the risk of serious injury. *See* Sauerland, *supra*, at 1136; Cincinnati Children's Hospital, *supra*. Clinicians may be discouraged from using veins in the hand and wrist for similar reasons. *See* Sauerland, *supra*, at 1136-37. Indeed, the dangers of extravasation are so closely identified with vesicants that the Oregon Board of Nursing defines extravasation only to mean "[i]nadvertent infiltration of vesicant solution or medication into surrounding tissue." Oregon State Board of Nursing, *Advisory Guidelines for Infusion Therapy* (Sept. 20, 2001), http://www.oregon.gov/OSBN/pdfs/policies/infusion2.pdf. In sum, though specific policies on administration of irritants and vesicants vary, clinicians regard the distinction between vesicants and

other drugs as significant, and modulate precautions accordingly.

Phenergan is not identified as a vesicant on its labeling. Instead, Phenergan labeling identifies it as a "known arteriolar irritant," and provides instructions for "administering any irritant drug intravenously." JA390. In practice, as an irritant, promethazine is usually administered via IV push through peripheral, rather than central, veins. *See* Institute for Safe Medication Practices ("ISMP"), *Action Needed to Prevent Serious Tissue Injury with IV Promethazine* (Aug. 10, 2006) ("*Action Needed*"), http://www.ismp.org/newsletters/acutecare/articles/20060810.asp; ISMP, *Promethazine Conundrum: IV Can Hurt More than IM Injection!* (Nov. 2, 2006) ("*Promethazine Conundrum*"), http://www.ismp.org/newsletters/acutecare/articles/20061102.asp; Paparella, *supra*, at 54-55. In fact, after ISMP referred to promethazine as a "known vesicant" in its August 2006 issue, it was forced to retract that characterization after readers pointed out that the labeling referred to promethazine as only an irritant. *See Promethazine Conundrum*, *supra*.

Thus, until recently, the dangers posed by Phenergan were not commonly known among clinicians. *See* Paparella, *supra*, at 55. As of 2006, there were few published reports of inadvertent intra-arterial injection or extravasation. *See* Keene, *supra*, at 966; Mark A. Malesker et al., *Extravasation of I.V. Promethazine*, 56 Am. J. Health-Sys. Pharmacy 1742 (1999) ("[A] search of the primary literature . . . produced no reports of extravasation of promethazine. Similarly, the manufacturer was unable to provide references to

published reports."). Paparella writes that "[e]mergency department nurses are asked frequently to give this medication intravenous push, yet many are unaware of the risks associated with this practice and the serious outcomes that may occur with intravenous administration." Paparella, *supra*, at 55. One nurse observed that nurses were "casual" about how they delivered promethazine intravenously. *See* Susan Hohenhaus, *An Informal Discussion of Emergency Nurses' Current Clinical Practice*, 31 J. Emergency Nursing 465 (2005). But though few reports had been published, in August 2006, ISMP reported its own analysis of individual accounts from different sources, concluding that "scores" of unpublished reports indicated that "patient harm may be occurring more frequently than recognized." *Action Needed*, *supra*; *see Promethazine Conundrum*, *supra* ("Promethazine extravasations that result in serious tissue damage are not rare; indeed, one in five respondents reported awareness of such an occurrence in their facility within the past 5 years.").[8]

In recent years, the dangers of promethazine have become publicized. The ISMP issued a warning about intravenous administration in August 2006, and pointed out that newer drugs such as Zofran, which did not exist when Phenergan was approved for sale, are safer than promethazine. The ISMP recommended that promethazine be contraindicated for IV use, or that

[8] The Director of the FDA Office of Pharmacoepidemiology and Statistical Science described ISMP as "one of most important sources [FDA] has for obtaining information on medication errors occurring in health systems." *ISMP Testimonials*, http://www.ismp.org/about/testimonials.asp.

precautions similar to those taken with vesicants be used (central venous administration, avoid hands and wrists). *See Action Needed*, *supra*. Some hospitals have labeled promethazine as a vesicant in their own formularies, even though the drug is only formally designated as an irritant. *See Promethazine Conundrum*, *supra*; Utah University Health Care, *Promethazine (Phenergan) Injection Classified as Vesicant* (Apr. 2005), http://uuhsc.utah.edu/pharmacy/alerts/87.html. In February 2007, the Veterans Health Administration issued a promethazine warning, ordering that local VHA facilities develop protocols for promethazine usage. *See* U.S. Dep't of Veterans Affairs, VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel, *National PBM Drug Guidance: Promethazine HCL Injection* (Feb. 2007), http://www.pbm.va.gov/VACenterForMedicationSafety-BulletinsAndNewsAlerts.aspx.

Ironically, after ISMP issued its August 2006 report on promethazine's dangers, FDA endorsed ISMP's report and linked to it on its website. *See* FDA, *Preventing Medical Errors: Severe Tissue Injury with IV Promethazine* (Dec. 2006), http://www.accessdata.fda.gov/psn/transcript.cfm?show=58#6. FDA considered ISMP's report so important that in February 2008, it reissued the warning to "repeat[] some of the most important safety issues that continue to pose a public health concern." FDA, *Severe Tissue Injury with IV Promethazine (December 2006)* (Feb. 2008), http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=72#5. In both notices, FDA reiterated the ISMP's characterization of promethazine as a "known vesicant."

C. Adverse Event Reports in the FDA Database

As ISMP concluded, despite the dearth of published accounts of injuries from promethazine, there are individual reports dating back many years. Wyeth, as manufacturer, was required to forward certain of these reports to FDA. 21 C.F.R. §314.80(c). FDA also receives reports from health care professionals and consumers. *See* Center for Drug Evaluation and Research ("CDER"), *Adverse Event Reporting System* ("AERS") (June 6, 2008), http://www.fda.gov/cder/aers/default.htm. Additionally, Wyeth was obligated to develop procedures "for the surveillance, receipt, evaluation, and reporting" of such injuries to FDA. 21 C.F.R. §314.80(b); *see* CDER, *Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* 3-4 (March 2005) ("CDER Guidance"), http://www.fda.gov/Cder/Guidance/6359OCC.pdf. Despite these obligations, no evidence was introduced at trial to suggest that Wyeth ever presented FDA with any surveillance or evaluation of the injuries caused by extravasation. As it turns out, even the most rudimentary analyses might have revealed the extent of the dangers posed by Phenergan, and triggered closer FDA scrutiny.

"Adverse event" reports submitted to FDA – individual reports of unwanted, negative consequences associated with medication – are publicly available in the AERS database. *See* http://www.fda.gov/cder/aers/default.htm. The database dates back to 1969, and each report identifies the drug, the adverse event, and the method of administration (though they do not distinguish between IV push and IV drip). However,

prior to November 1997, the database employed a medical dictionary called COSTART, which recognized only 1,200 terms. Because terms were so limited, reports were coded in ways that were not always fully descriptive. For example, COSTART did not utilize the term "amputation"; instead, reports of amputation might be coded as "gangrene," if applicable. After November 1997, FDA changed its database to AERS from the older Spontaneous Reporting System and switched to MedDRA, an expanded classification schema containing approximately 20,000 terms. After the adoption of MedDRA, AERS recognized the term "amputation." *See generally* FDA, *MedDRA: Medical Dictionary for Regulatory Activities*, http://www.fda.gov/Medwatch/report/meddra.htm.

Using AERS, the frequency of injuries associated with intravenous administrations of Phenergan (and generic versions) can be examined. In pharmacoepidemiology, one simple way to determine whether a reaction is associated with a particular drug is by calculating the "proportional reporting rate" ("PRR") of the reaction. *See* Brian Strom, *Pharmacoepidemiology* 180-81 (3d ed. 2000); CDER Guidance at 9. The PRR demonstrates whether the adverse reaction under study represents a greater proportion of all adverse reactions for the subject drug than for comparable drugs. To calculate the PRR, the researcher determines the percentage of times the adverse reaction under study has occurred relative to other adverse reactions. This percentage is then compared to the percentage of times the reaction has occurred, relative to other reactions, in other drugs. For example, the researcher may find that out of 10 reported adverse events for a given drug, 5, or 50%,

involve hallucinations. In a comparable drug, the researcher may find that out of 20 adverse events, 5, or 25%, involve hallucinations. The PRR is 50% divided by 25%, or 2. *See* Strom, *supra*, at 180-81. A second calculation, known as the "chi-square," is then performed. Chi-square is a standard statistical measurement that expresses the degree to which two proportions differ from what one would expect given random chance. *See* Stanton A. Glantz, *Primer of Biostatistics* 113-163 (5th ed. 2002).[9] Though many factors may be relevant, a PRR of 2 or more, coupled with a chi-square of 4 or more, is generally considered a "signal" requiring further investigation. *See* Strom, *supra*, at 180-81.

Wyeth, with its access to adverse event data, could easily have performed these basic calculations to compare intravenous promethazine with other intravenous medications and determine whether injuries similar to Respondent's appeared at a high rate. For example, according to AERS, from 1969 through November 1997 (when the database and dictionary changed) there were 307 reported "serious" adverse events associated with promethazine administered

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[9] For example, if two drugs are equally associated with hallucinations, no matter how many adverse event reports are submitted for each drug, the same percentage of each will involve hallucinations. A chi-square is used to measure the extent to which the actual percentages differ from this perfectly equal outcome. Chi-square is defined as "a quantity equal to the summation over all variables of the quotient of the square of the difference between the observed and expected values divided by the expected value of the variable." Random House Webster's Unabridged Dictionary 362 (2d ed. 2001).

intravenously. Of those, 4 (1.30%) were coded as gangrene.[10] During the same period, there were 77,693 reported "serious" adverse events associated with all other medications administered intravenously, with 121 (0.155%) coded as gangrene. Had Wyeth examined this data, it would have calculated a PRR of 8.4 with a chi-square of 25 – a strong signal.

After the adoption of MedDRA, coders could indicate amputations in addition to, or instead of, gangrene. From December 1997 through December 2006, there were 468 serious adverse events associated with intravenous promethazine, of which 11 (2.35%) were coded as gangrene and 20 (4.27%) were coded as amputations. For the same period, 144,346 serious adverse events were reported for all other intravenously-administered medications, of which 111 (0.077%) resulted in gangrene and 213 (0.15%) resulted in amputations.[11] These figures yield a PRR of 30.5 for gangrene and 29 for amputations, with chi-squares of *286* and *494*, respectively – powerful signals of promethazine's dangers.

Additionally, as explained above, promethazine has been associated with injuries besides gangrene and

[10] Because PRR is dependent on voluntary submission of adverse reaction reports, it is inherently vulnerable to underreporting. *See* Phil B. Fontanarosa et al., *Postmarketing Surveillance – Lack of Vigilance*, *Lack of Trust*, 292 JAMA 2647 (2004); Amalia M. Issa, et al., *Drug Withdrawals in the United States: A Systematic Review of the Evidence and Analysis of Trends*, 2 Current Drug Safety 177, 182-83 (2007).

[11] These data cannot be aggregated; a single patient may experience both gangrene and amputation.

amputation. Several of these are identified in the August 2006 ISMP warning, such as nerve damage, paralysis, phlebitis, and tissue necroses. *See Action Needed*, *supra*. The MedDRA offers several alternative terms for these reactions and classifies them as related.[12] Had Wyeth analyzed serious adverse events associated with intravenous promethazine between 1969 and November 1997, it would have discovered that 45% (138 of 307) involved reactions related to those in the August ISMP report.[13] By contrast, 13% (10,099 of 77,693) of serious adverse events reported for other intravenous drugs involved reactions related to the ISMP report reactions, for a PRR of 3.46, with a chi-square of 274 — a clear signal of problems with intravenous promethazine.

Expanding the analysis, from 1969 through December 2006, 45.6% (354 out of 775) of the serious adverse event reports for intravenous promethanzine involved reactions related to those listed in the August ISMP report. By contrast, 15.7% (34,905 of 222,039) of serious adverse events reported for other intravenous

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[12] MedDRA is a four-level hierarchical scheme. Terms within the same high-level group are related to one another. For example, "vasculitis," which refers to several different diseases concerning inflammation of the blood vessels, and "phlebitis," are both under the same high level group term "Vascular Inflammations." *See generally* Int'l. Fed'n. of Pharm. Mfrs. and Ass'ns., *Medical Dictionary for Regulatory Activities Introductory Guide Version 11.0* (2008).

[13] Because the coding system allows for a single patient to be recorded as having experienced several types of tissue damage from a single incident, these data have been "deduped" so that each identified instance of a reaction represents a single patient.

drugs involved reactions MedDRA classifies as related to the ISMP report reactions, for a PRR of 2.9, with a chi-square of 520. Once again, although these numbers do not distinguish IV drip from IV push, at minimum, they create a warning signal that should have triggered further investigation.

Ultimately, however the specific data are interpreted, there is no evidence that Wyeth ever performed these basic and simple tests fundamental to postmarketing surveillance, let alone any of the more sophisticated analyses available to it. In other words, FDA may have generally known that there had been reports of gangrene and tissue necrosis, but there is no evidence that Wyeth even attempted to communicate to FDA (or physicians) the frequency and severity of these risks.[14] Nor was it FDA's responsibility to mine its own data regarding each drug on the market. *See* 21 C.F.R. §314.80(b) (placing responsibility for postmarket surveillance on the manufacturer); CDER Guidance. Though the United States claims that FDA, and not the manufacturer, has the responsibility to "decide when safety information should be included in the labeling for a product," U.S. Br. 23 (quotations omitted), in fact, primary responsibility for the label at all times rests with the manufacturer. *See* 21 C.F.R. §201.80(e) ("The labeling *shall* be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug." (emphasis added)) (older drugs); 21 C.F.R. §201.57(c)(6)(i) ("the

[14] FDA itself has stated that "new" information allowing manufacturers to change labeling without prior FDA approval includes information about frequency or severity of known risks, or new analyses of older data. *See* 73 Fed. Reg. 2848, 2850 (2008).

labeling *must* be revised" (emphasis added)) (newer drugs). Thus, there are strong indications that Wyeth failed to meet regulatory obligations, and that FDA failed to consider a significant source of information when examining Phenergan.

D. Supplying Physicians with Accurate Information

As the above discussions show, there has been a stark divergence between the medical profession's understanding of Phenergan's risks, and the actual dangers the drug poses. As a matter of simple communication, the FDA-approved label has been insufficient to inform doctors of the relevant risks. This is why the United States is incorrect to argue that under federal regulations, manufacturers are prohibited from strengthening warnings without "new information" suggesting risks of "a different type or greater severity than risks of which FDA had previously been made aware." U.S. Br. 24.[15] There are a variety of reasons why an FDA-approved label might not fully protect patients, including the real possibility that FDA may not anticipate how the drug is *actually used*, or how the labeling is interpreted by clinicians.[16] Manufacturers, not FDA,

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[15] This definition is apparently narrower than the definition of "new" adopted by FDA. *See* 73 Fed. Reg. at 2850.

[16] There is evidence that both industry and FDA are slow to react even when clinicians flatly misunderstand labeling. According to the Institute of Medicine, between 2000 and 2007, several organizations, including the Centers for Disease Control and ISMP, notified FDA that thousands of patients were at risk of injury due to repeated confusion over the similar labeling of

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have the best access to this information, including information about drug marketing and usage, which is why the statutory and regulatory scheme places responsibility on them to monitor adverse events and strengthen safety and dosage information. *See* 21 C.F.R. §§201.57(c)(6)(i), 314.80.[17]

The United States's argument that state courts will undermine FDA's "careful balancing of risks and benefits" is beside the point. U.S. Br. 22. Respondent is not advocating that States determine when a product

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two different drugs. *See* Institute of Medicine of the National Academies, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* 279 (2007) ("Institute of Medicine Report"). "For about a year, the response by industry and the FDA to the error notification was that 'providers should read the label.' …When the manufacturer sent the FDA a revised label for approval, it remained at the agency for 6 months without action being taken." *Id.*

[17] The United States argues that the approval process would be "undermined" if the regulations were interpreted to allow manufacturers "to make unilateral changes to labeling the day after FDA's approval based on information that was previously available." U.S. Br. 21. This argument ignores the actual context in which these regulations arise – namely, one in which manufacturers routinely resist stronger warnings. FDA had no reason to draft its regulations to protect against an overwarning manufacturer, because such manufacturers do not exist. As this Court stated in *Geier v. American Honda Motor Co., Inc.*, 529 U.S. 861 (2000), "[W]hy should DOT have bothered to impose an airbag ceiling when the practical threat to the mix it desired arose from the likelihood that manufacturers would install, not too many airbags too quickly, but too few or none at all?" *Id.* at 880.

is defective and should be removed from the market despite the benefits it provides to other patients; Respondent seeks only to insure that doctors receive sufficient information to perform their *own* balancing of risks against benefits for their individual patients – a task they are required to perform by the ethics of their profession.[18] There is no reason why such information cannot be presented in a truthful manner that accurately conveys the degree of risk while still leaving the product available to those who need it.[19]

The United States nonetheless argues that, even with full trial protections, a jury, and the likely review of State appellate courts, States will impose "excessive warnings" that will "cause more meaningful risk information to lose its significance" and will "limit physician appreciation of potentially far more significant risks." U.S. Br. 17, 19 (quotations omitted). But this argument "rest[s] solely on the offensive assumption that the public will respond 'irrationally' to the truth."

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[18] FDA's interpretation of the preemptive scope of its labeling regulation would extend not only to claims against the manufacturer, but also to claims against the *doctor* for failing to warn of risks not identified in the labeling. *See* 71 Fed. Reg. 3922, 3836 (2006). In other words, FDA claims it is empowered not only to regulate *products*, but also to regulate the *medical profession* and standards of practice.

[19] The United States also fails to consider that the risks and benefits of a drug may change due to the introduction of newer, safer alternatives. Even if, for example, IV push administration of an anti-nausea drug is necessary for some patients, it may be that after the introduction of safer alternatives, the risks of Phenergan become unacceptably high.

44 Liquormart v. R.I., 517 U.S. 484, 503 (1996). This Court has repeatedly

> reject[ed] the notion that the Government has an interest in preventing the dissemination of truthful commercial information in order to prevent members of the public from making bad decisions. . . . [The] alternative is to assume that this information is not in itself harmful, that people will perceive their own best interests if only they are well enough informed, and that the best means to that end is to open the channels of communication rather than to close them.

Thompson v. W. States Med. Ctr., 535 U.S. 357, 374 (2002).

FDA, as well, has said that physicians should be supplied with all available information so that doctors may make their own informed judgments about the product. For example, since the labeling format revisions, FDA has required that drug labels warn for hazards associated with *other* drugs in the same class, even when the hazard has not been associated with the subject drug. *E.g.*, 21 C.F.R. §201.57(c)(7)(i). In 1979, FDA rejected one commenter's concern that these requirements, as well as the warning requirements generally, would "mislead" physicians, stating:

> The Commissioner does not agree that physicians will be misled by clear and concise statements in prescription drug labeling regarding serious hazards associated with the use of a drug or a listing of adverse reactions

> that occur with the drug or drugs of the same chemical or pharmacological class. The Commissioner believes that practicing physicians will welcome such information so that they can make their best informed medical judgments in the care of their patients.

44 Fed. Reg. 37,434, 37,447 (1979). In other words, FDA recognized that physicians are capable of understanding and assimilating factual, truthful information about a drug's theoretical risks, even when such risks have never materialized.

Nor is there evidence that "the threat of significant damage awards or penalties" will pressure manufacturers to "propose 'defensive labeling,'" as FDA seems to fear. 71 Fed. Reg. at 3935. After FDA noticed a proposal to alter the standards for a manufacturer to strengthen safety information on drug labeling, 73 Fed. Reg. 2,848, several members of Congress, including Representative Henry A. Waxman, Senator Christopher J. Dodd, and Senator Patrick J. Leahy, directed FDA to "describe any cases" in which the manufacturer strengthened warnings, contraindications, precautions, or adverse reactions "in a manner that harmed public health." Letter from Hon. Henry Waxman et al. 4 (Jan. 23, 2008). In response, FDA evaluated label changes received since 2004, and was unable to identify a *single instance* in which a manufacturer had unduly strengthened its warnings; instead, it named three instances in which a manufacturer's proposed changes were rejected as *not strong enough*, and one instance where FDA requested additional data supporting the change, after which it was approved. *See* Letter from Stephen Mason, FDA, to Hon. Henry Waxman 3-4 (Mar. 7, 2008).

In fact, FDA has repeatedly said that warnings required by labeling rules do not represent the sum total of all warnings that a manufacturer may issue, or may be required to issue. In connection with the labeling format revisions, FDA went out of its way to stress that "labeling regulations do not prohibit a manufacturer, packer, relabeler, or distributor from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered. The addition to labeling and advertising of additional warnings, as well as contraindications, adverse reactions, and precautions regarding the drug, or the issuance of letters directed to health care professionals . . . is not prohibited by these regulations." 44 Fed. Reg. at 37,447. FDA even cited with approval *McEwan v. Ortho Pharmaceutical Corp*., 528 P.2d 522 (Or. 1974), which held that FDA labeling requirements represent a minimum duty of disclosure, and that States may impose duties beyond mere compliance with FDA regulations. 44 Fed. Reg. at 37,447.

Manufacturers continue to be permitted to send "Dear Doctor" letters, which warn clinicians of hazards associated with particular drugs. There is no rule requiring that such letters only contain information identical to that in the product labeling, nor is there a requirement that they be reviewed by FDA prior to distribution so long as they are submitted to FDA after mailing. The only content restriction is that the letter may not be false, misleading, or unfair. *See* CDER, *Manual of Policies and Procedures: NDAs: "Dear Health Care Professional" Letters* (July 2, 2003), http://www.fda.gov/Cder/mapp/6020.10.pdf. Once again, this practice demonstrates that FDA is not overly concerned with the possibility of "overwarning."

Further, the United States's argument that uncontrolled warnings will "limit physician appreciation of potentially far more significant risks" is belied by the existence of FDA's own website, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/, which provides a steady stream of new safety warnings, many of which do not appear in product labeling, and have not, apparently, undergone formal agency "balancing" of risks relative to benefits. Among other things, the website contains notifications when FDA is merely *investigating* potential hazards, even if the "information is preliminary" and there is "scientific uncertainty." FDA, *FDA Studying Potential Safety Issues with Several Drugs* (June 2008), http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=76#2. After a published article found higher mortality for a particular drug, FDA announced that until it completed its own evaluation, physicians should be aware of the information in the study *in addition* to the "risks and benefits" in the labeling. FDA, *Early Communication About an Ongoing Safety Review* (Nov. 14, 2007), http://www.fda.gov/cder/drug/early_comm/cefepime.htm.[20] And in the Food and Drug Administration Amendments Act of 2007, Congress ordered FDA to make publicly available on the internet an extensive amount of information about the risk profile of each drug, including summaries of certain adverse event data, with no requirement that such information first be approved for

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[20] *See also* FDA, *Early Communication About an Ongoing Safety Review* (Feb. 2008), http://www.fda.gov/cder/drug/early_comm/botulinium_toxins.htm ("FDA is considering, but has not reached a conclusion about whether this information warrants any regulatory action.").

inclusion in labeling. *See* Pub. L. 110-85, §915. In actuality, then, both Congress and FDA have consistently sought to give health care practitioners access to as much accurate information as possible regarding potential hazards, without fear that such information will impede physician appreciation of "more significant risks."

II. COSTS ASSOCIATED WITH DANGEROUS DRUGS

By one estimate, 30% of hospitalized patients experience an adverse drug event. *See* Sandra Kane-Gill et al., *Adverse-Drug-Event Rates for High-Cost and High-Use Drugs in the Intensive Care Unit*, 63 Am. J. Health-Sys. Pharmacy 1876 (2006). Anywhere from 85% to 90% of adverse drug reactions experienced by hospitalized patients are caused by drugs that are "properly" administered, i.e., appropriately prescribed at the correct dosage. *See* Bonnie L. Senst et al., *A Practical Approach to Determining Costs and Frequency of Adverse Drug Events in a Health Care Network*, 58 Am. J. Health-Sys. Pharmacy 1126 (2001); A. Elixhauser and P. Owens, *Adverse Drug Events in U.S. Hospitals*, HCUP Statistical Brief #29 (Apr. 2007), http://www.hcup-us.ahrq.gov/reports/statbriefs/sb29.pdf. Adverse drug reactions increase the length of hospital stays by approximately 2 days, with additional costs to the patient of $1,900 to $7,000. *See* Kane-Gill, *supra*, at 1877; Senst, *supra* at 1127. One study of four hospitals run by the University of New Mexico found that among adverse reactions occurring in hospitalized

patients, 19% were life-threatening, 45% were serious, and 36% were significant. *See* Senst, *supra*, at 1130. Another study found that the costs of drug-related problems among outpatients exceeded $177.4 billion, more than twice the estimate of $76.6 billion in 1995, and more than the costs of medications themselves. *See* F.R. Ernst & A.J. Grizzle, *Drug-Related Morbidity and Mortality: Updating the Cost-of-Illness Model* 41 J. Am. Pharmaceutical Ass'n 192 (2001). And from 1998 through 2005, serious adverse drug events reported to FDA increased 260%, a rate four times faster than the number of outpatient prescriptions written during this period. *See* Thomas J. Moore et al., *Serious Adverse Drug Events Reported to the Food and Drug Administration*, 1998-2005, 167 Archives Internal Med. 1752 (2007). Seventeen percent resulted in fatalities. *See id.* at 1754.

A substantial portion of the costs of these injuries are ultimately borne by third-party payors, such as Medicare and Medicaid, insurance companies, union-based health and welfare funds, and employer sponsored health benefit plans. Adverse drug reactions thus have the potential to have a tremendous impact on the costs of healthcare. However, when an adverse drug reaction can be shown to have been caused, in whole or in part, by the manufacturer's failure to warn of foreseeable risks, third party payors' reimbursement and subrogation rights can serve as a critical mechanism for cost-containment, holding down both healthcare costs and premium expenses. Though precise figures are unavailable, it can be estimated that third-party payors

recover well in excess of $1 billion annually through reimbursement and subrogation.[21]

On average, 1.5 drugs per year were withdrawn from the market over safety concerns between 1993 and 2006, a figure that does not include drugs that increased their warnings or limited their indications. *See* Issa, *supra*, at 179. It is impossible to know the total costs associated with unsafe medications, but there is anecdotal evidence that they are substantial. For example, in January 2006, the New England Journal of Medicine reported that Trasylol, a drug to reduce bleeding during cardiac surgery, drastically increased the risk of kidney failure, heart attacks, and strokes for certain patients. *See* Dennis Mangano et al., *The Risk of Aprotinin in Cardiac Surgery*, 354 New Eng. J. Med. 353 (2006). The article estimated that dialysis costs attributable to Trasylol – on the market since 1993 with an expanded indication in 1998 – were $1 billion a year, and that had patients been prescribed cheaper, safer generics, $250 million annually would have been saved. *See id.* FDA took months to react, questioned the researcher's methodologies, and voted to keep Trasylol on the market

[21] During fiscal year 2003, Trover Solutions, Inc., a claims-recovery service, reported recoveries of $239.5 million for 40 million lives insured. *See* Trover Solutions, Inc., 2003 Form 10-K, at 29. Today, 250 million Americans have health insurance, and health care costs rose 18% per capita between 2003 and 2006. *See* Carmen DeNavas-Walt, et al., U.S. Census Bureau, *Income, Poverty, and Health Insurance Coverage in the United States: 2006* (Aug. 2007), http://www.census.gov/prod/2007pubs/p60-233.pdf; Kaiser Family Foundation, *National Health Expenditures Per Capita, 1995-2006* (May 2008), http://facts.kff.org/chart.aspx?ch=203.

even after learning that Bayer, the manufacturer, had failed to disclose a study of 67,000 patients that confirmed Dr. Mangano's results. *See* Kris Hundley, *Drug Warnings Fall Flat*, St. Petersburg Times, Aug. 5, 2007, at 1A. Trasylol was ultimately withdrawn in November 2007 when a Canadian study was halted after preliminary results showed Trasylol increasing the risk of death. *See* Mike Stobbe, *2 More Studies Link Drug to Deaths*, Deseret Morning News, Feb. 21, 2008, at A6.

Vioxx, approved in 1999 and prescribed to 80 million people before it was recalled in 2004, provides another example. *See* Eric J. Topol, *Failing the Public Health — Rofecoxib, Merck, and the FDA*, 351 New Eng. J. Med. 1707 (2004). By one estimate, Vioxx caused between 88,000 and 139,000 sudden heart attacks or deaths. *See FDA, Merck and Vioxx: Putting Patient Safety First? Hearing Before the S. Comm. on Finance*, 108th Cong. 14 (2004) (statement of Dr. David J. Graham). In April 2008, the Journal of the American Medical Association reported that Merck had waged an intentional campaign to distort the results of its clinical trials and to present company research as independent in order to conceal Vioxx's risks from FDA. *See* David Brown, *Maker of Vioxx is Accused of Deception*, Wash. Post, Apr. 16, 2008, at A1. In 2007, Merck agreed to settle lawsuits filed by patients and their family members for $4.85 billion. *See id.*

Petitioner's amici argue that, in most instances, patients and their insurers, rather than drug manufacturers, should be forced to bear the costs of injuries associated with drugs found to carry insufficient

warnings. *E.g.*, Brief of John E. Calfee et al. 16. But manufacturers are far better positioned to bear the costs of injuries caused by their products. Manufacturers, with their superior risk information, are best able to take precautions. Further, in 2006, the pharmaceuticals industry was the second most profitable in the country, second only to mining/crude oil production, and was more than three times as profitable as the median for all Fortune 500 companies. *See* Kaiser Family Foundation, *Profitability of Pharmaceutical Manufacturers Compared to Other Industries*, 1995-2006 (Jan. 2008), http://facts.kff.org/chart.aspx?ch=218. Meanwhile, national health expenditures per capita rose nearly 47% from 2000 to 2006. *See* National Health Expenditures, *supra*.

Petitioner's amici contend that drug manufacturers hesitate to introduce new, beneficial medications for fear of crushing liabilities. *E.g.*, Calfee Br. 16. But there is scant evidence of pharmaceutical companies' hesitancy. Even though drug manufacturers have always been exposed to State tort liability, *see Riegel v. Medtronic, Inc.*, 128 S.Ct. 999, 1019 (2008) (Ginsburg, J., dissenting), they continue to take risks both in their development of new drugs and their marketing of them. For example, direct to consumer advertising increased 330% between 1996 and 2005, despite the widespread view that aggressive marketing of newer drugs, before there is sufficient data about their safety profile to enable patients and doctors to make informed decisions about them, can result in unnecessary injuries to patients. *E.g.*, Julie M. Donahue, *A Decade of Direct-to-Consumer Advertising of Prescription Drugs*, 357 New Eng. J. Med. 673, 674, 678-79 (2007); R.L. Kravitz

& R.A. Bell, *Direct-to-Consumer Advertising of Prescription Drugs: Balancing Benefits and Risks, and a Way Forward*, 82 Clinical Pharmacology & Therapeutics 360, 361 (2007). Despite these risks, and the associated risks of liability, most direct to consumer advertising begins within a year of the drug's introduction. *See* Donahue, *supra*, at 678-79. In fact, according to the Institute of Medicine, pharmaceutical labeling today poses risks to patient health not because of "overwarning" or "defensive warning," but because, among other things, labels may contain "extraneous, unnecessary commercial information" and "[o]veremphasis on company logos and trade dress." Institute of Medicine Report, *supra*, at 276-77.

In short, whatever inhibitions pharmaceutical companies may feel about bringing new drugs to market in the face of uncertain liabilities, they are apparently far outweighed by manufacturers' desire to create markets for their products. For this reason, there is no reason to upset the balance between federal and State regulation of pharmaceuticals that has existed virtually unchanged since 1962.

CONCLUSION

Phenergan presents an example of how insufficient manufacturer vigilance, coupled with lax regulatory oversight, can leave doctors critically uninformed of serious risks to their patients. It is precisely because tragic situations like these are all too common that, for decades, courts have recognized that both States and FDA have important roles to play in overseeing drug safety. If States are stripped of that role, patients' health will be put in jeopardy, with corresponding increases in the cost of medical care. The decision of the Vermont Supreme Court should be affirmed.

Respectfully submitted,

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